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EXAMINER	
LU, FRANK WEI MIN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,383	LOFTON-DAY ET AL.	
	Examiner	Art Unit	
	FRANK LU	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8, 10, 11, 20-39, 41-43, 45-51, 53, 55, and 57-60* is/are pending in the application.

4a) Of the above claim(s) *5,6,46-51,53,55 and 57-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,10,11,20-39,41-43,45 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/23/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on February 28, 2011 has been entered. The claims pending in this application are claims 1-8, 10, 11, 20-39, 41-43, 45-51, 53, 55, and 57-60 wherein claims 5, 6, 46-51, 53, 55, and 57-59 have been withdrawn due to restriction requirement mailed on October 7, 2009 and the election of species mailed on April 13, 2010. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on February 28, 2011. Claims 1-4, 7, 8, 10, 11, 20-39, 41-43, 45, and 60 will be examined.

Election/Restrictions

2. This application contains claims 46-51, 53, 55, and 57-59 drawn to an invention nonelected with traverse in the reply filed on January 7, 2010. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. Receipt is acknowledged of papers submitted on March 29, 2011 under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

4. Claim 2 is objected to because of the following informality: "the ALX 4 gene sequence" should be "ALX 4 gene sequence". Note applicant does not address this issue.

5. Claim 3 is objected to because of the following informality: "the ALX 4 gene" in comparing step should be "ALX 4 gene".

6. Claim 4 is objected to because of the following informality: "the ALX 4 gene" should be "ALX 4 gene".

7. Claim 21 is objected to because of the following informality: "comprising" in line 2 of step b) should be deleted.

8. Claim 33 is objected to because of the following informality: "the at least one hybridized nucleic acid molecule or peptide nucleic acid molecules" should be "at least one of the hybridized nucleic acid molecules or peptide nucleic acid molecules".

9. Claim 34 is objected to because of the following informality: "substantially linear, substantially hexagonal or substantially rectangular and combinations thereof" should be "substantially linear array or substantially hexagonal array or substantially rectangular array or combinations thereof".

10. Claim 35 is objected to because of the following informality: "at least one hybridized nucleic acid molecule" should be "at least one of the hybridized nucleic acid molecules".

11. Claim 37 is objected to because of the following informality: "the primers of a)" should be "the primers of b)".

12. Claim 43 is objected to because of the following informality: "the primer oligonucleotide of c)" should be "the primer of b)".

13. Claim 45 is objected to because of the following informality: "sequences that hybridize under stringent conditions thereto" in step c) should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. New Matter

Claims 3, 4, and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitation "comparing the ALX 4 gene (SEQ ID NO:5) expression level in the sample with the expression level from a subject not having a colon cell proliferative disorder, wherein reduced expression of the ALX 4 gene (SEQ ID NO:5) in the sample as compared with the sample from the subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder" is added to the newly amended independent claim 3. Although the specification describes that "increased or decreased levels of expression of said genes or sequences are associable with the development of colorectal carcinoma and other colorectal cell proliferative disorders"(e.g., see page 28, last paragraph bridging to page 29, first paragraph), paragraphs [0027] and [0105] to [0109] of the specification suggested by applicant fail to define or provide any disclosure to support such claim recitation since the phrase "is indicative of a colon cell proliferative disorder" recited in claim 3 and phrase "are associable with the

development of colorectal carcinoma and other colorectal cell proliferative disorders" described in the specification have totally different meanings.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

16. Enablement

Claims 1-4, 7, 8, 10, 11, 20-39, 41-43, 45, and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention</u>

The claims are drawn to a method for detecting a colon cell proliferative disorder in a human subject. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.,* 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claims 1, 2, and 60 encompass a method for detecting a colon cell proliferative disorder in a human subject by contacting genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells obtained from the subject with at least one reagent that distinguishes between methylated and non-methylated CpG dinucleotide sequences within ALX4 gene sequence (SEQ ID NO:5) and comparing the CpG methylation status of a gene in the sample with the CpG methylation status of the gene in any kind of sample from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status between the gene in the sample and the gene in any kind of sample from a subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder. Claim 2 further limits claim 1 and requires that CpG dinucleotide sequences comprises at least 16 contiguous nucleotides of ALX 4 (SEQ ID NO:5) gene sequence. Claim 60 further limits claim 1 and requires that the detection of the colon cell proliferative disorder has a sensitivity of greater than or equal to 80% and a specificity of greater than or equal to 80%. Claims 3, 4, and 7 encompass a method for detecting a colon cell proliferative disorder in a human subject by determining the expression levels of the ALX 4 gene (SEQ ID NO:5) or gene sequences thereof, in a sample from the subject comprising colon cells, colon fluid, stool, or colon tissue; and comparing the ALX 4 gene (SEQ ID NO:5) expression level in the sample with the expression level from a

subject not having a colon cell proliferative disorder, wherein reduced expression of the ALX 4 gene (SEQ ID NO:5) in the sample as compared with the sample from the subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder. Claim 4 further limits claim 3 and requires that said expression level is determined by detecting the presence, absence or level of mRNA transcribed from ALX 4 gene (SEQ ID NO:5). Claim 7 further limits claim 3 and requires that the expression level is determined by detecting the presence or absence of CpG methylation within the gene or gene sequence thereof. Claims 8, 10, 11, 21-39, and 41-43 encompass a method for detecting a colon cell proliferative disorder in a human subject by contacting genomic DNA or a fragment thereof from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue obtained from the subject with at least one reagent that distinguishes between methylated and non-methylated CpG dinucleotide sequences with at least one target region, wherein the at least one target region comprises, or hybridizes under stringent conditions to 9 contiguous nucleotides sequence of ALX 4 gene sequence (SEQ ID NO: 5), and the contiguous nucleotides comprise at least one CpG dinucleotide sequence, and comparing the CpG methylation status in the sample with the CpG methylation from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder. Claim 20 encompasses a method for detecting a colon cell proliferative disorder in a human subject comprising contacting genomic DNA or a fragment thereof from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue with at least one reagent that distinguishes between methylated and non-methylated CpG dinucleotides, and amplifying at least one target sequence of the DNA with at least one primer pair, wherein the

target sequence comprises, or hybridizes under stringent conditions to an at least 16 contiguous nucleotide sequence of a sequence selected from the group consisting of SEQ ID NOs:5, 312, 313, 428, and 429 and a complement thereof, wherein the contiguous nucleotide sequence comprises at least one CpG dinucleotide sequence. Claim 45 encompasses a method for detecting a colon cell proliferative disorder in a human subject by contacting the genomic DNA or a fragment thereof, extracting or isolating from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue, comprising at least 16 contiguous nucleotides of SEQ ID NO:5 and sequences that hybridize under stringent conditions thereto, with one or more methylation-sensitive restriction enzymes, wherein the genomic DNA is, either cleaved thereby to produce cleavage fragments, or not cleaved thereby, determining the CpG methylation status of SEQ ID NO:5, or an average, or a value reflecting an average methylation state status of a plurality of CpG dinucleotides of a target CpG dinucleotide sequences within SEQ ID NO:5 and comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder.

Working Examples

The specification provides no working example related to the claimed invention recited in claims 1-4, 7, 8, 10, 11, 20-39, 41-43, and 45.

The Amount of Direction or Guidance Provided and The State of The Prior Art

The specification does not provide guidance for the methods recited in claims 1-4, 7, 8, 10, 11, 20-39, 41-43, and 45. Furthermore, there is no experimental condition and/or experimental data in the specification to support the claimed invention recited in claims 1-4, 7, 8, 10, 11, 20-39, 41-43, and 45. Although it is known in the art that that "age-related methylation is a common event in human tissue" (see page 351, left column, second paragraph from Seminars in Cancer Biology, 9, 349-357, 1999) and "[M]ethylation changes in cancer include hypomethylation of overall genomic DNA as well as regional hypermethylation involving CpG islands" (see page 349, right column, second paragraph from Seminars in Cancer Biology, 9, 349-357, 1999), and ALX 4 gene methylation is a potential marker for colorectal adenocarcinomas (Gastroenterology, 131, 1418-1430, 2006), during the process of the prior art search, the examiner has not found any prior art which is related to the claimed invention recited in claims 1-4, 7, 8, 10, 11, 20-39, 41-43, and 45.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether the methods recited in claims 1-4, 7, 8, 10, 11, 20-39, 41-43, and 45 can be performed.

First, since it is known that "age-related methylation is a common event in human tissue" (see page 351, left column, second paragraph from Seminars in Cancer Biology, 9, 349-357, 1999), "[M]ethylation changes in cancer include hypomethylation of overall genomic DNA as well as regional hypermethylation involving CpG islands" (see page 349, right column, second

paragraph from Seminars in Cancer Biology, 9, 349-357, 1999), age-related CpG island methylations vary in different human individuals (see page 3798, right column and Figure 3 from Clin. Cancer Res., 13, 3796-3802, 2007), and claim 1 does not limit the CpG methylation status to the CpG methylation status of ALX4 gene and does not indicate how to differentiate colon cell proliferative disorder related CpG methylation from age-related CpG methylation, it is unclear how a difference in the CpG methylation status between any kind of gene in a sample from a human subject and said gene in any kind of sample from any kind of subject not having a colon cell proliferative disorder can be indicative of a colon cell proliferative disorder so that the detection of the colon cell proliferative disorder has a sensitivity of greater than or equal to 80% and a specificity of greater than or equal to 80% as recited in claims 1, 2, and 60 and cannot indicate that the human subject is a subject with old age. For example, it is known that CpG methylation of estrogen receptor gene has been found in both normal aged colon mucosa and colon cancer (see page 350, right column from Seminars in Cancer Biology, 9, 349-357, 1999). Furthermore, since it is known that ALX4 methylation is also frequently observed in adenocarcinomas of the esophagus, stomach, and bile ducts, it is unclear how a difference in the CpG methylation status between any kind of gene in the sample and said gene from any kind of subject not having a colon cell proliferative disorder can be indicative of a colon cell proliferative disorder so that the detection of the colon cell proliferative disorder has a sensitivity of greater than or equal to 80% and a specificity of greater than or equal to 80% as recited in claims 1, 2, and 60 and cannot indicate adenocarcinomas of the esophagus, stomach, and bile ducts when the genomic DNA is from blood plasma, blood serum, whole blood, or isolated blood cells. In addition, since claim 1 does not require that a subject not having a colon cell

proliferative disorder is a human subject and the CpG methylation status from the subject not having a colon cell proliferative disorder is generated from genomic DNA of blood plasma, blood serum, whole blood, or isolated blood cells, it is unclear how to perform the methods recited in claims 1, 2, and 60 by comparing the CpG methylation status in the sample with the CpG methylation status from any kind of sample from any kind of subject not having a colon cell proliferative disorder as recited in claims 1, 2, and 60.

Second, although ALX4 gene is expressed in colon cancer cell lines (see page 2689, right column from Cancer Epidemol. Biomakers Prev., 16, 2686-2696, 2007), since it is known that ALX4 gene is expressed in both stromal and luminal epithelial cells in a normal human breast and a loss of ALX4 in stromal and epithelial cells in breast tumor is observed (see abstract from Journal of Clinical Pathology, 62, 908-914, 2009) and the specification does not show that ALX4 expression can be detected in colon cells, colon fluid, stool or colon tissue of a human subject, it is unclear how reduced expression of the ALX 4 gene (SEQ ID NO:5) in a human sample as compared with a sample from a subject not having a colon cell proliferative disorder can be indicative of a colon cell proliferative disorder as recited in claims 3, 4, and 7 and cannot be indicative of breast tumor wherein the sample from the subject comprises colon cells, colon fluid, stool or colon tissue of a human subject. Furthermore, since claim 3 does not require that a subject not having a colon cell proliferative disorder is a human subject and the ALX4 expression level from the subject not having a colon cell proliferative disorder is generated using a sample comprises colon cells, colon fluid, stool or colon tissue, it is unclear how to perform the methods recited in claims 3, 4, and 7 by comparing ALX4 gene (SEQ ID NO:5) expression level in the sample with ALX4 gene expression level of any kind of sample from any kind of subject

not having a colon cell proliferative disorder. In addition, since the expression level of a gene is related to mRNA or protein level of the gene and is not related to CpG methylation, it is unclear how the expression level of ALX4 gene is determined by detecting the presence or absence of CpG methylation within the gene or gene sequence thereof as recited in claim 7.

Third, since the phrase "the at least one target region comprises, or hybridizes under stringent conditions to 9 contiguous nucleotides of the ALX 4 gene sequence (SEQ ID NO: 5), and the contiguous nucleotides comprise at least one CpG dinucleotide sequence" in claim 8 is read as "a target region comprises, or hybridizes under stringent conditions to 9 contiguous nucleotides of the ALX 4 gene sequence (SEQ ID NO: 5) and the contiguous nucleotides comprise one CpG dinucleotide sequence" and the at least one target region may be from other gene which is not human ALX 4 gene (SEQ ID No:5). Since it is known that human kinase (PRKA) anchor protein 8 gene contains 9 contiguous nucleotides of human ALX 4 gene sequence (5'-GGGCCGGGG-3', nucleotides 85-93 of SEQ ID No:5) (see sequence comparison between human kinase (PRKA) anchor protein 8 gene and human ALX 4 gene) and the specification does not show to compare the CpG methylation status of human kinase (PRKA) anchor protein 8 gene in the sample with the CpG methylation of human kinase (PRKA) anchor protein 8 gene from a subject not having a colon cell proliferative disorder, it is unclear how a difference in the CpG methylation status of the at least one target region (ie., human kinase (PRKA) anchor protein 8 gene) comprising or hybridizing under stringent conditions to a sequence of 9 contiguous nucleotides of ALX 4 gene sequence can be indicative of a colon cell proliferative disorder as recited in claims 8, 10, 11, and 21-42. Furthermore, although claim 21 requires contacting the treated genomic DNA, or the treated fragment thereof, with an

amplification enzyme and at least two primers comprising that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOs:312, 313, 428 and 429, since claim 21 does not indicate how to differentiate an amplificate amplified from methylated genomic DNA and an amplificate amplified from unmethylated genomic DNA, it is unclear how the methylation state of at least one CpG dinucleotide of a sequence selected within of SEQ ID NO:5, or an average, or a value reflecting an average methylation state of a plurality of CpG dinucleotides can be determined based on a presence or absence of, or on a property of said amplificate so that a difference in the CpG meth1ation status can be indicative of a colon cell proliferative disorder by comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder as recited in claims 21-39 and 41-43. In addition, since claim 21 does not require that a subject not having a colon cell proliferative disorder is a human subject and the CpG methylation status from the subject not having a colon cell proliferative disorder is generated from genomic DNA of blood plasma, blood serum, whole blood, or isolated blood cells, it is unclear how the methods recited in claims 21-39 and 41-43 can be performed by comparing the CpG methylation status in the sample with the CpG methylation status from any kind of sample from any kind of subject not having a colon cell proliferative disorder.

Fourth, since claims 31, 41, and 42 require hybridizing at least one nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOs:312, 313, 428 and 429, if the nucleic acid molecule is "TTTTTTTTTT" from SEQ ID NO: 313 or 429 which can hybridize polyA sequence of many different mRNAs, a specific

hybridization complex for human ALX 4 gene cannot be formed so that the methods of claims 31, 41, and 42 cannot be performed.

Fifth, since claim 20 does not indicate how to correlate steps a) to c) with detecting a colon cell proliferative disorder, it is unclear that, in which situation, a colon cell proliferative disorder can be detected. Furthermore, since the phrase "the target sequence comprises, or hybridizes under stringent conditions to an at least 16 contiguous nucleotide sequence of a sequence selected from the group consisting of SEQ ID NOS:5, 312, 313,428, and 429 and a complement thereof, wherein said these contiguous nucleotide sequence comprises at least one CpG dinucleotide sequence" is read as "the target sequence comprises, or hybridizes under stringent conditions to 16 contiguous nucleotide sequence of a sequence selected from the group consisting of SEQ ID NOs:5, 312, 313,428, and 429 and any complement thereof, wherein said these contiguous nucleotide sequence comprises one CpG dinucleotide sequence" and the target sequence may be from other gene which is not one of SEQ ID Nos:5, 312, 313, 428, and 429. Since it is known that human kinase (PRKA) anchor protein 8 gene contains 16 contiguous nucleotides of SEQ ID No:5 (5'- GGGGCCGGGGCCAGGG-3', nucleotides 84-99 of SEQ ID No:5) (see sequence comparison between human kinase (PRKA) anchor protein 8 gene and human ALX 4 gene) and the specification does not show to compare the CpG methylation status of human kinase (PRKA) anchor protein 8 gene in the sample with the CpG methylation of human kinase (PRKA) anchor protein 8 gene from a subject not having a colon cell proliferative disorder, it is unclear how a difference in the CpG methylation status of the at least one target region (ie., human kinase (PRKA) anchor protein 8 gene) comprising or hybridizing under stringent conditions to an 16 contiguous nucleotides of a sequence selected from the group

consisting of SEQ ID NOs:5, 312, 313,428, and 429 and a complement thereof can be indicative of a colon cell proliferative disorder as recited in claim 20.

Sixth, since the phrase "the genomic DNA of b), or a fragment thereof, comprising at least 16 contiguous nucleotides of SEQ ID NO:5" in claim 45 is read as "the genomic DNA of step b) or a fragment thereof comprising 16 contiguous nucleotides of SEQ ID NO:5" and the genomic DNA of step b) or a fragment thereof may be from other gene which is not one of SEQ ID No:5. Since it is known that human kinase (PRKA) anchor protein 8 gene contains 16 contiguous nucleotides of SEQ ID No: 5 (5'- GGGGCCGGGGCCAGGG-3', nucleotides 84-99 of SEQ ID No: 5) (see sequence comparison between human kinase (PRKA) anchor protein 8 gene and human ALX 4 gene) and the specification does not show to compare the CpG methylation status of human kinase (PRKA) anchor protein 8 gene in the sample with the CpG methylation of human kinase (PRKA) anchor protein 8 gene from a subject not having a colon cell proliferative disorder, it is unclear how the CpG methylation status of SEQ ID NO:5, or an average, or a value reflecting an average methylation state status of a plurality of CpG dinucleotides of target CpG dinucleotide sequences within SEQ ID NO:5 can be determined and how a difference in the CpG methy1ation status can be indicative of a colon cell proliferative disorder by comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder as recited in claim 45. Furthermore, since claim 45 does not require that a subject not having a colon cell proliferative disorder is a human subject and the CpG methylation status from the subject not having a colon cell proliferative disorder is generated from genomic DNA of blood plasma, blood serum, whole blood, or isolated blood cells, it is unclear how the method recited in claim 45 can be performed

by comparing the CpG methylation status in the sample with the CpG methylation status from any kind of sample from any kind of subject not having a colon cell proliferative disorder.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. The undue experimentation at least includes to test whether the methods recited in claims 1-4, 7, 8, 10, 11, 21-39, 41-43, and 45 can be performed.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working example related to the claimed invention and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

In page 18, last paragraph bridging to page 19, first paragraph of applicant's remarks, applicant argues that the office rejects the claims by "citing Seminars in Cancer Biology, 9, 349-357, 1999 in support of its position. Applicants respectfully submit that the cited reference indicates (see Abstract) 'in colorectal cancer, there appears to be two types of methylation that

are associated with cancer progression: type A (for age-related) methylation, and type C (for cancer specific methylation). Initially, type A methylation arises as a function of age [but] result[s] in a predisposition state that precedes tumor formation in the colon.' When taken in context, the reference cited by the Office does not raise a question of distinguishing between age-related methylation and methylation associated with colorectal cancer given that all types of CpG methylation described by the reference have a direct correlation with cancer progression. The reference merely states that type A methylation is *initially* age-dependent but precedes tumor formation in the colon. Furthermore, paragraph [0265] in Example 1 of the results section of the specification states '[s]pecificity of the panel in asymptomatic individuals over 50 years of age was 91%,' wherein specificity is described at paragraph [0018] of the specification as follows: '[s]pecificity, on the other hand, is a measure of a test's ability to identify accurately patients who are free of the disease state. A test having poor specificity produces a high rate of false positives, *i.e.,* individuals who are falsely identified as having the disease.' Therefore, the data contained specification clearly indicate that false positives *i.e.,* in practice there was a low incidence of subjects prone to age-related methylation and presenting aberrant methylation but not having a colon cell proliferative disorder".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because the claims do not indicate how to differentiate colon cell proliferative disorder related CpG methylation (type C methylation) from age-related CpG methylation (type A methylation).

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1, 2, 8, 10, 11, 21-39, 41-43, 45, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. Claim 1 is rejected as vague and indefinite in view of step c) because the phrase "comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder" does not make sense. Does this phrase mean that "comparing the CpG methylation status of ALX4 gene in the sample with the CpG methylation status of ALX4 gene from a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, or isolated blood cells of a human subject not having a colon cell proliferative disorder, wherein a difference between the CpG methylation status of ALX4 gene in the sample and the CpG methylation status of ALX4 gene from the biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, or isolated blood cells of a human subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder"? Please clarify.

20. Claim 2 is rejected as vague and indefinite because it is unclear that the CpG dinucleotide sequence in the claim means methylated CpG dinucleotide sequence or unmethylated CpG dinucleotide sequence. Please clarify.

21. Claim 8 is rejected as vague and indefinite in view of step c) because the phrase "comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder" does not make sense. Does

this phrase mean that "comparing the CpG methylation status of ALX4 gene in the sample with the CpG methylation status of ALX4 gene from a biological sample comprising genomic DNA from a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue of a human subject not having a colon cell proliferative disorder, wherein a difference between the CpG methylation status of ALX4 gene in the sample and the CpG methylation status of ALX4 gene from the biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue of a human subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder"? Please clarify.

22. Claim 21 is rejected as vague and indefinite because it is unclear how to correlate step b) of claim 20 with steps a) to d) of claim 21 and it is unclear that steps a) to d) of claim 21 is happened before or after which step of claim 20. Please clarify.

23. Claim 21 or 45 is rejected as vague and indefinite in view of step d) because the phrase "comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder" does not make sense. Does this phrase mean that "comparing the CpG methylation status of ALX4 gene in the sample with the CpG methylation status of ALX4 gene from a biological sample comprising genomic DNA from a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue of a human subject not having a colon cell proliferative disorder, wherein a difference between the CpG methylation

status of ALX4 gene in the sample and the CpG methylation status of ALX4 gene from the biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue of a human subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder"? Please clarify.

24. Claim 21 is rejected as vague and indefinite because it is unclear where a plurality of CpG dinucleotides is located. Please clarify.

25. Claim 23 is rejected as vague and indefinite because use of a heat resistant DNA polymerase as the amplification enzyme or use of a polymerase lacking 5'-3' exonuclease activity or use of a polymerase chain reaction (PCR) or generation of amplificate nucleic acid molecule carrying a detectable label is not considered as a method. Please clarify.

26. Claim 26 recites the limitation "the at least 9 contiguous nucleotides of b)" in the claim. There is insufficient antecedent basis for this limitation in the claim because there is no "at least 9 contiguous nucleotides" in step b) of claim 21 and claim 20. Please clarify.

27. Claim 28 or 29 recites the limitation "the nucleic acid molecule or peptide nucleic acid molecule" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no phrase "nucleic acid molecule or peptide nucleic acid molecule" in claims 20, 21, and 26. Please clarify.

28. Claim 41 is rejected as vague and indefinite because it is unclear that at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence

selected from the group consisting of SEQ ID NOS:312, 313,428 and 429 hybridizes to what. Please clarify.

29. Claim 42 is rejected as vague and indefinite because it is unclear that at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOs: 312, 313, 428 and 429 and complement thereof hybridizes to what. Please clarify.

Conclusion

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

31. No claim is allowed.

32. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Frank W Lu /
Primary Examiner, Art Unit 1634
May 4, 2011